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# TRANSLATION MEDICINE AND BIOMARKERS; BENCH TO BEDSIDE—AN OVERVIEW

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## ABSTRACT

There is no clear definition of translational medicine; it means different things to different people. Here, we define translational medicine (also referred to as translational science) as a rapidly growing discipline in biomedical research that aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative approach. Often described as the practice of transferring scientific knowledge "from bench to bedside" (B2B), translational medicine builds on fundamental research advances–studies of biological processes using cell cultures, for example, or animal models – and uses them to develop new therapies or medical procedures. Translation science is often described as an effort to carry scientific knowledge, "From bench to bedside." Translation medicine builds on necessary research advances studies of the biological process using cell cultures or animal models and uses them to develop therapies or medical procedures. The main feature of translation medicine is the bridging function between preclinical and clinical research. It aims at answering the single but tremendously important question. If a drug X works in rats, rabbits, and even monkeys, how likely will it be beneficial to humans? Historically, how did this simple and straightforward question, which naturally inherent to all drug development processes, become of primary relevance biochemical research? (1). The term "Bench to Bedside" is used to describe the process by which the results of the study done in the laboratory use to develop new ways to treat patients, according to the National Cancer Institute (NCI) dictionary. This term is not new. The idea that clinical and basic scientists could work at the interface between basic science and clinical medicine and lead to significant breakthroughs has existed for a long time (2). Every novel discovery begins with a burning question and evolves through a journey that starts with experiments in the laboratory. To translate laboratory research into a clinical application as a new methods of diagnosis, treatment, or prevention is the big challenge, and that is where translational research steps. The European Society defines translational research for Translational Medicine (EUSTM) as an interdisciplinary branch of the biomedical field supported by three main pillars: bench-side, bedside, and community (3). Despite tremendous efforts and the cloning of the entire genome, innovations at the patient level are becoming rare events and insufficiency in predicting human efficacy or safety of new drugs from early discovery and development work blamed for many failures. It is a complex science and needs careful development both as a science and concrete projects. The majority of translation research relies on preclinical animal models. However, an incredible number of examples of failed. There is no single ideal animal model of human disease conditions.

**KEYWORDS:** From bench to bedside (B2B), Second translational block (T2) National Centre for Advancing Translational Science (NCATS), Biomarkers, Bioethics Genome,

**INTRODUCTION:**

One prime example of translational research in human disease is the study of cancer therapy. Extensive cooperation between basic researchers, clinicians, and industry has generated numerous new targeted compounds with enhanced efficacy and decreased toxicity. In addition to the development of new anti-cancer agents, translational research can also be applied to predicting response to therapy and resistance and sensitizing cancer cells to current therapeutics (4). Translational Research describes a continuum of study wherein scientific discoveries are integrated into clinical applications, and conversely, clinical applications are used to generate research foci for basic science: the "bench to bedside and back to bench" approach. (5) Translational research comes with its own set of challenges. It incorporates aspects of both basic science and clinical research and requires skills and resources that are not readily available in a basic laboratory or an exclusively clinical setting. To achieve this, clinics and laboratories have to be linked to each other. This can be a daunting task, with several barriers and challenges. There are inherent cultural differences between basic scientists and clinicians including differences in education and training that may affect collaborations and result in a lack of communication. Other hurdles include a lack of resources in terms of workforce and infrastructure and the presence of regulatory issues (6). The next several decades saw a rapid increase of new therapeutic agents, including anti-metabolites, DNA damaging agents, as well as the introduction of combination therapy. Indeed, most efforts at cancer therapy involve direct interference with cell proliferation by altering events that occur during the cell cycle, as cell growth is unregulated, mainly in cancer cells. Early chemotherapy focused on inhibiting cell growth through mitotic poisons to control tumor cell proliferation (7).

Ionizing radiation (IR) is a critical cancer therapy that has been widely used since its efficacy was first demonstrated over a century ago. IR utilizes high-energy radiation to kill cancer cells by inducing lethal DNA damage and is often used in conjunction with either surgery or chemotherapy (8). Although radiation therapy is generally well tolerated, secondary cancers, skeletal complications, radiation-induced heart disease, and lung disease are common side effects (9). Very few treatments were tested in preclinical studies make their way into clinical trials of 5000 compounds tested in animals. Approximately five will show enough promise in human trials for a company to file an Investigational New Drug Application with the US Food and Drug Administration.(10) The European Society defines translational medicine for Translation Medicine (EUSTM) as "an interdisciplinary branch of the biomedical field supported by three main pillars: bench side, bedside, and community " (11). It is defined for school-based education by the Education Futures Collaboration as research that translates concepts to classroom practice (12). Examples of translational research are commonly found in education subject association journals and in the MESH Guides, which have been designed for this purpose (13). Cross-sectional developed biomarkers and review the advantages, principles, and position of prospective tissue bio marking in translation research. Atherosclerotic tissue biomarking highlights as an example of a well-established initiative towards multifactorial disease for a multifactorial approach (14).

Drug safety and efficacy vary considerably among patients and few molecular or clinical factors that might help better to predict an individuals' response to a given drug. Many patients will experience the desired drug effect; some may suffer from well known adverse reactions (ADRs). Others may experience no consequences, and very recently, a patient will die from severe effects. It is currently confusing to physicians to prescribe the optimal drug in the optimal dose for each patient because the prediction of a patient's response to any of the specific drug is rarely possible (15). Animal model of cancer, and in particular genetically engineered mouse models, has significantly contributed to the understanding of tumor biology and cancer pathophysiology. (16) There is no single ideal animal model of human disease conditions. Likewise, the design of the preclinical, experimental studies at present offers substantial room for improvement. (17) The use of animal models mimic human hypertensive situations is valuable information in understanding the different routes of pathophysiology and therapeutic interventions. In experimental hypertension research, several animal models exist, and rats are the most commonly used animals (18). In the study of atherosclerosis, the mouse is the most frequently used species. Nevertheless, heart

rate, total cholesterol, sites of atherosclerosis, and the development time differ between mice and humans (19). Rodent models of cerebral ischemia are good examples of animal models that replicate human pathophysiology as well (20).

**A CHRONOLOGICAL RECORD OF SIGNIFICANT EVENTS:**

Transitional medicine is a rapidly growing discipline in biomedical research and aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative, "bench-to-bedside" approach.[Within public health, translational medicine is focused on ensuring that proven strategies for disease treatment and prevention are actually implemented within the community. One prevalent description of translational medicine, first introduced by the Institute of Medicine's Clinical Research Round table, highlights two roadblocks (i.e., distinct areas in need of improvement): the first translational block (T1) prevents basic research findings from being tested in a clinical setting; the second translational block (T2) prevents proven interventions from becoming standard practice (21). The National Institutes of Health (NIH) has made a significant push to fund translational medicine, especially within biomedical research, with a focus on cross-functional collaborations (e.g., between researchers and clinicians); leveraging new technology and data analysis tools, and increasing the speed at which new treatments reach patients. In December 2011, The National Centre for Advancing Translational Science (NCATS) was established within the NIH to "transform the translational science process so that new treatments and cures for disease can be delivered to patients faster."

The Clinical and Translational Science Awards, established in 2006 and now funded by NCATS, supports 60 centers across the country that provide "academic homes for translational sciences and supporting research resources needed by local and national research communities." According to an article published in 2007 in Science Career Magazine, from 2007 to 2013, the European Commission targeted a majority of its €6 billion budget for health research to further translational medicine (22). Translational medicine or translational science in the field of medicine has attracted considerable recent attention. It grew from the concerns that the explosion of basic biomedical science was not being translated into meaningful improvements in patient care or not being accomplished in an expeditious manner commensurate with the large expenditures in research and the growing needs to treat patients or prevent disease occurrence (23). The problems facing the translation of medical science from basic research to widespread clinical practice have been described and discussed (24). Barton and colleagues document through meticulous research, the many physicians and scientists who advanced the field to that point from where Andreas Guntzig made his leap forward (25)

This kind of information pays tribute to individuals whose significant contributions were the essential foundation of the field. It also recalls the medieval comment, later made famous by Sir Isaac Newton, that one sees further standing "on the shoulder of giants." Besides, the advancement of coronary angioplasty required several individuals who recognized the value of the work being done by Andreas Gruntzig and permitted him to proceed with his plans without necessarily directly contributing to the intellectual property of coronary angioplasty. Barton and colleagues document, the contribution of these facilitators and colleagues as well (26) Biographies are usually written about individuals who have fascinated us because of their accomplishments, opinions, or legacy. Although Western civilization recognizes the stories of the lives of biblical persons as well Greek and Roman philosophers and leaders, English literature attributes the first English biography to that of Samuel Johnson by James Boswell because of the detailed research which formulated the description of Samuel Johnson and the objectivity with which it was written (27)

**LITERATURE GAP AND FUTURE RESEARCH:**

The first translation gap was in the translation of ideas from research into the development of new products and therapies, and the second gap was the uptake of evidence-based treatments in routine clinical practice. It's well documented in the pharmaceutical sector that the path from discovery to clinical adoption and use of a new commercial product is long and dangerous. It can take many years (sometimes more than 20 years) to bring a new product to the market where it can benefit patients. Everyone involved in medical research would like to see biomedical research discoveries turned into a more patient benefit – sooner, more often and in more diverse areas. With this aim in mind, in 2008, the MRC set out to improve the translation of UK academic medical research. The characterization of the BRCA1 gene in 1994 and other genes associated with cancer suggested immediate applications in the early detection and treatment of diseases. Yet, almost a decade later, the National Institutes of Health's "Roadmap for Medical Research" highlighted critical scientific gaps that were blocking or delaying the translation of discoveries in the life sciences into improvements in medical care (28).

The salience of this so-called translational gap was secured by a 2008 article suggesting that the gap between biomedical research and improvements in medical care had become an abyss in which breakthrough discoveries went to die, a hole called the Valley of Death. Understanding the source of the translational gap requires appreciating the role of randomized controlled trials. Randomized controlled trials have been useful for establishing the benefits of therapies or devices because they are considered the method most likely to generate valid results. Nevertheless, numerous problems have been noted. One question central to the translational gap is referred to by Deaton and Cartwright as the transportation problem. They argue that if the average treatment effect of a randomized controlled trial is, by chance, close to the truth, then the revelation referred to is for the trial sample alone. There is no guarantee that the average treatment effect of a randomized controlled trial would apply to other patients who were not eligible for the examination or who were otherwise excluded from the trial. How does context created by an individual's biology and biography (life experience) account for the transportation problem and lead to the translational gap? (29).

**ADVANCED DISCOVERIES IN TRANSLATION RESEARCH:**

The Institute of Medicine's Clinical Research Round table highlighted two translational blocks that prevent discoveries of promising drugs, diagnostic technologies, or therapeutic procedures that are generated by basic research from getting translated into clinical applications (30). Success is not the norm, even for research with the most promising results. For primary research that ultimately leads to patient applications, the interval is long, often more than ten years. Several explanations for the lag were proposed: funding sustainability through the tedious discovery to the application process, difficult challenges of validating and ensuring that the product is safe and effective, competing for research priorities, and a lack of trained translational investigators and participants to carry on research (31). It initiates the search using any "intervention" (drug, chemical, target molecule, gene locus, test, etc.) or a specific disease process or condition (autism, asthma, cataract, obesity) or narrows the search using both (prostate cancer, thrombotic thrombocytopenic purpura, ADAMTS-13, diabetes, and a thiazolidinedione, etc.). The search results list up to 100 of the most recent citations on each page, depending on the publication date selected. Links are provided to earlier quotes if more than 100 are found. Using RxNorm, a standardized nomenclature for clinical drugs, and Medical Subject Heading (MeSH) classification of diseases, the retrieved PubMed IDs (PMID) are sorted into "Interventions" and "Diseases." Abstracts that are not in either one of the two headings are listed separately. PMIDs may be duplicated in the "Disease" or "Intervention" category. Search terms, interventions, and diseases are highlighted in the abstract (32).

**A NOVEL TOOL FOR TRANSLATIONAL RESEARCH DISCOVERY:**

Advances in biology are occurring at a breathtaking pace today, from genetic insights facilitated by the Human Genome Project and next-generation DNA sequencing technologies to global nucleic acid and proteomic expression measurement using new high-throughput methods. Less publicized in recent years, yet still, the central driver of progress is the steadily proceeding biological insights gained through the tried and true hypothesis-driven investigation into the complex worlds of metabolism, growth, development, and regulation. Indeed, the underlying science ecosystem is productive, and this portends well for the myriad new applications that will benefit humanity; drugs, vaccines, devices, and related economic growth (33).

**INTELLECTUAL PROPERTY IN TRANSLATIONAL MEDICINE AND BIOMEDICAL RESEARCH:**

Translational medicine intends to find faster, less expensive and more effective ways to translate basic research into clinical applications. Intellectual property can contribute to making this transition. Intellectual property provides to the medical translation process, including details about patents both in general and about specific medical tools and products (34). Translation medicine advances medical science by facilitating the translation of basic research into clinical applications that would ultimately benefit patients. This translation requires rigorous scientific research. Sufficient funding, timely and appropriate business decision, compliance with regulatory systems and legal and ethical frame works, extensive communication and net working among the different parties and product development. Biomedical research has many different facets. Researchers and clinicians study disease biology and biochemistry to discover novel therapeutic targets, unravel biochemical pathways, and identify biomarkers to improve diagnosis or devise new approaches to manage diseases more useful clinically. In all instances, the overall goal of biomedical research is to ensure that results thereof (such as a therapy, a device, or a method which may be broadly referred to as "inventions") are clinically implemented. Most of the researchers' efforts are centered on the advance of the technical and scientific aspects of an invention. The development and implementation of a design can be arduous and very costly (35). Intellectual property rights (IPR) have been defined as ideas, inventions, and creative expressions based on which there is a public willingness to bestow the status of the property. IPR provides certain exclusive rights to the inventors or creators of that property to enable them to reap commercial benefits from their creative efforts or reputation. There are several types of intellectual property protection, like patent, copyright, trademark, etc. A patent is a recognition for an invention, which satisfies the criteria of global novelty, non-obviousness, and industrial application. IPR is a prerequisite for better identification, planning, commercialization, rendering, and thereby protection of invention or creativity (36).

**TRANSLATIONAL RESEARCH IN THE FASTEST-GROWING POPULATION: (OLDER ADULTS):**

Aging is the most critical risk factor for the vast majority of chronic conditions that lead to disability and death, and account for the bulk of health care costs in developed countries. Translation research in aging has the potential to influence not only life span, but health span—the number of years one spends in health,

free from disease, or disability. Animal models and human cohorts are useful in translational research in aging, but essential limitations exist and influence experimental design, interpretation of results findings (37). Translational research in aging has the potential to change life span and health span beyond the boundaries of traditional disease-based research. There are many animal models and human cohorts that are useful in studying aging, but essential limitations include marked differences among them that make translating animal finding to social difficult a number of key limitations that affect longitudinal studies in both human and animals, and the need to study multimorbidity and complexity for translation research to be generalizable to most older adults.

**BIOMARKERS DISCOVERY IN TRANSLATIONAL RESEARCH:**

The field of biomarker discovery has exhibited a significant surge of interest in recent years. Biomarkers can be used for many purposes, including diagnosis, prognosis, and selecting appropriate patient therapy, and can provide information on disease mechanism or progression. Translation of such markers to clinical testing encompasses phases for their discovery and characterization, assay development, and finally, implementation using automated platforms employed in clinical laboratories (38). Biomarkers may be apparent measures such as blood pressure or heart rate in humans or less visible means such as hair color or cell cycle stages, gene polymorphous, life or death, and ability to fertilize and produce offspring. In biomedical sciences, it is helpful to focus the definition of biomarkers on their operation as critically selecting what to look at or measure is indispensable if scientific approaches to drug or medical device development are to succeed (39). Hypertension is one of the most common cardiovascular disorders over the age of 60 years; around 60%-70% of the population is affected. Antihypertensive drugs are still among the most prescribed medications by clinicians. Despite all the available treatment options, disease management is still not adequate. Only 50% of patients with hypertension have their blood pressure appropriately regulated below (140/90 mm Hg) (40). In experimental hypertension research, several animal models exist, and rats are the most commonly used animals (41).

**RECENT ADVANCES IN DIAGNOSTIC TECHNOLOGY:**

Improving therapeutic strategies involving existing treatments is a prime concern for now. Patient variation, concerning treatment response (efficacy an addition to the identification of potential diagnostic applications, we have a significant focus on identifying new treatment targets, and/nd toxicity), is a well-documented phenomenon (42). Through the capturing of clinical data and pertinent samples across a large patient population that exhibits variable treatment response, retrospective statistical analysis of the integrated clinical, experimental and molecular data could reveal the underlying causes of this variation. For example, DNA polymorphisms in some isoforms of the cytochrome p450 enzymes have been associated with the difference in the rates of metabolism of many pharmaceutical drugs across a sample population (43). It focuses on the various aspects of translational research, where research on human subjects can ultimately enhance the diagnosis and treatment of future patients. While we will use specific examples relating to the asbestos-related cancer mesothelioma, it should be stressed that the general approach outlined throughout this review is readily applicable to other diseases with an underlying molecular basis. Through the integration of molecular-based technologies, systematic tissue procurement, and medical informatics, we now can identify clinically applicable "genotype"-"phenotype" associations across cohorts of patients that can rapidly be translated into useful diagnostic and treatment strategies (44).

**RESEARCH PROGRAM FOR THE NEXT GENERATION WORLD:**

Translational medicine is a rapidly growing discipline in biomedical research. It aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative, "bench-to-bedside" approach. Translational medicine converts promising laboratory discoveries into clinical applications and attempts to answer clinical questions with the use of bench work to facilitate prediction, prevention, diagnosis, and treatment of diseases. In other words, translational medicine transforms the essential investigation achievements of medical biology into practical theory, technology, and methods that will bridge laboratory and clinical practice.

**TRANSLATIONAL MEDICAL RESEARCH--FUTURE DIRECTIONS AND CHALLENGES:**

Translational medicine thus involves three main pillars, the bench side, the bedside, and the community. Its primary aim is to translate fundamental biomedical research into clinical applications using a multidisciplinary, highly collaborative, 'bench-to-bedside' approach that will benefit patients and the community at large. In the USA and Europe, formal translational research centers promote such research and highlight its necessity in creating a competent health care system. In Kuwait, although no precise translational research center and active researchers are already involved in translational medicine. Four faculty seminars were selected to showcase the impact of basic science research and its likely translation into clinical practice (45).

**TRANSITIONAL RESEARCH AND NEED OF NEW BIOETHICS:**

Translational research tries to apply findings from basic science to enhance human health and well-being. Many phases of translational research may include non-medical tasks (information technology, engineering, nanotechnology, biochemistry, animal research, economy, sociology, psychology, politics, and so on). Using universal bioethics principles to these areas might sometimes be not feasible or even impossible. However, the whole process must respect some fundamental moral principles (46).

**TRANSLATION MEDICINE CARE AND MANAGEMENT:**

Translational Medicine's principal goal is to speed the development of new compounds of medical protocols and treatments to improve the patient's quality of life. The medicine calls for synergy between epidemiology, primary research, and clinical trials and firmly based on innovation management and research development in medicine. For this reason, a managerial view of translational medicine is particularly prolific in terms of insights for researchers and clinicians who place efforts to improve health service (47). Recently there is a growing awareness about the role of translational medicine for the improvement of patient outcomes (48). Reducing human disease and mortality is, in fact, the end purpose in which translational medicine is generally and commonly recognized (49). Translational medicine success is directly correlated to innovation since innovation and technology transfer affect health services, linking the quality of care to continuous improvement and translational medicine prolific research contexts. Change in health contexts results from both scientific and technological progress and often is strictly depending on their reciprocal inferences. Health innovation is the result of both biomedical research (genomics, neuroscience, molecular oncology, etc.) and technology (medical diagnostics, biotechnology, health informatics, electronic devices, etc.). Consider, e.g., the following innovation advances in health fields. Proteomic, Bimolecular-diagnostic, Pharmacogenetics, and Diagnostic imaging (50).

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both human and animals, and the need to study multimorbidity and complexity for translation research to be generalizable to most older adults.

**CURRENT ALTERCATION IN TRANSLATION MEDICINE:**

Concurrent to the recent research advancements in the development of nanomaterials, there has been a substantial effort to translate some of the most promising nanomaterials from bench to bedside. Analysis of issued patents related to nano-bio materials indicates this trend. The use of nano-bio materials in developing nano-carriers for drug delivery is bringing a great deal of hope and enthusiasm in the field of drug delivery research. Nanoscale drug delivery devices present some advantages, as they show higher intracellular uptake than conventional drug delivery systems. Meanwhile, these nanostructures can also be modified with chemical and/or biochemical moieties, which bind specifically to the targeted tissues for better confinement of the treatment to the diseased tissues. Besides their function for targeted drug delivery, some nanostructures can act as active anticancer therapeutics as a result of their inherent optical and dielectric properties, magnetic susceptibility, and thermal or electrical conductivity. Nano-carriers can be conjugated with a ligand, such as an antibody, to favor a targeted therapeutic approach (51).

**SUMMARY OF TRANSITIONAL RESEARCH:**

Most aging patients have multiple concurrent health problems. However, most current medical practice and research are primarily based on a single disease model, failing to account for the simultaneous presence of multiple conditions. Clinical trials, practice guidelines, and pay-for-performance schemes may thus have limited applicability in older patients (52). The National cancer institute, Experimental Therapeutics (NExT) program is designed to assist investigators in "bench to bedside" translation of novel anticancer therapeutics interventions, synthetic, natural product, or biologic, arising from academic, industrial, or government entities. The program provides the resources for selected discovery tasks, complete pre-clinical IND-enabling tasks, and biomarker development for Phase 0 clinical studies. The jobs are completed by NCI staff and contractors, rather than through direct investigator grants. The program goal is to provide NCI with an integrated pre-clinical pipeline of novel anticancer agents (53)

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